A Convenient Synthesis of 3-Alkyl-4-aminobutanoic Acids

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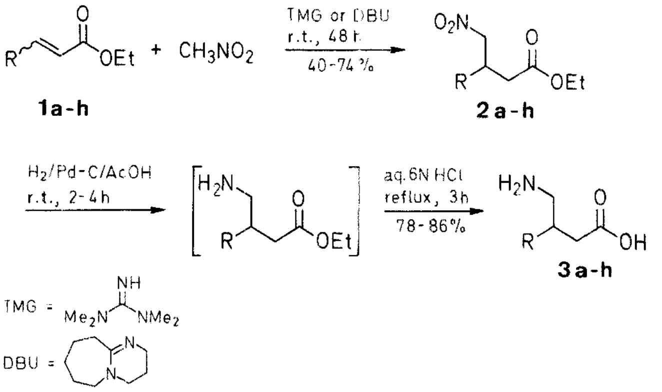
A series of 3-alkyl-4-aminobutanoic acids were prepared via the Michael addition of nitromethane to 2-alkenoic esters, followed by catalytic hydrogenation of the resultant 3-(nitromethyl)alkanoic esters using 10% palladium on carbon in acetic acid, and acid hydrolysis of the reduction products.

γ-Aminobutyric acid (GABA) analogues, as substrates and inhibitors of γ-aminobutyric acid aminotransferase (E.C.2.6.1.19), have been extensively studied in this laboratory.[1] In continuation of this program we required ready access to 3-alkyl-4-aminobutanoic acids for our investigations. Surprisingly, only a few reports on the synthesis of these amino acids have appeared.[2-4] For example, 3-methyl-4-aminobutanoic acid was prepared by the Michael addition of nitromethane to methyl crotonate, followed by high-pressure hydrogen-



1, 2, 3	R	1, 2, 3	R
a[a]	CH_3	e	n-C_4H_9
b	C_2H_5	f	s-C_4H_9
c	n-C_3H_7	g	i-C_4H_9
d	i-C_3H_7	h	t-C_4H_9

[a] Commercially available ethyl crotonate (**1a**) was used.

ation on Raney-nickel at elevated temperature.[3-4] 3-Ethyl- and 3-propyl-4-aminobutanoic acids were synthesized from the corresponding nitroalkenes and dimethyl malonate: the resulting 4-nitroesters were reduced by Raney nickel hydrogenation to give the corresponding 2-pyrrolidones which were acid-hydrolyzed to the GABA analogues.[4] This route suffers from certain disadvantages, including high-pressure hydrogenation and the limited accessibility of the required nitroalkenes.

We report here a method for the formation of 3-alkyl-4-aminobutanoic acids **3a–h** starting from 2-alkenoic esters **1a–h**, which can be easily prepared from commercially available aldehydes and monoethyl malonate by the Knoevenagel reaction,[5] with the exception of ethyl 4,4-dimethyl-2-pentenoate (**1h**). This compound was prepared from 2,2-dimethylpropanal and ethyl lithioacetate,[6] followed by dehydration of the β-hydroxyester with phosphoryl chloride and pyridine.[7] The Michael addition of nitromethane to α,β-unsaturated compounds mediated by 1,1,3,3-tetramethylguanidine[8] or 1,8-diazabicyclo[5.4.0]undec-7-ene[9] (DBU) afforded 4-nitroesters **2a–h** in good yields (Table 1). The relatively low yield of **2h** is probably associated with the steric hindrance by the bulky *tert*-butyl group in compound **1h** during the reaction with nitromethane.

Table 1. Compounds **2a–h** Prepared

Compound	Yield[a] (%)	bp (°C)/ Torr	Molecular Formula[b] or Lit. bp (°C)/Torr	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)
2a	74	84–86/2	84–86/1[14]	1.07 (d, 3H, J = 7); 1.35 (t, 3H, J = 6.50); 2.36 (d, 2H, J = 6); 2.5–2.8 (m, 1H); 4.20 (q, 2H, J = 6.5); 4.22–4.5 (m, 2H)
2b	70	106–108/ 2	$C_8H_{15}NO_4$ (189.2)	1.06 (t, 3H, J = 6.5); 1.33 (t, 3H, J = 7); 1.45–1.65 (m, 1H); 2.4–2.7 (m, 3H); 4.22 (q, 2H, J = 7); 4.52 (d, 2H, J = 6)
2c	64	110–112/ 1.25	98–100/ 1.5[15]	0.9 (t, 3H, J = 6); 1.26 (t, 3H, J = 7); 1.3–1.5 (m, 4H); 2.4 (d, 2H, J = 6.5); 2.5–2.8 (m, 1H); 4.14 (q, 2H, J = 7); 4.46 (d, 2H, J = 6)
2d	72	115–116/ 1.25	$C_9H_{17}NO_4$ (203.2)	0.95 (d, 6H, J = 6.5); 1.28 (t, 3H, J = 7); 1.65–1.95 (m, 1H); 2.45–2.75 (m, 3H); 4.13 (q, 2H, J = 7); 4.45 (d, 2H, J = 6)
2e	65	124–126/ 1.25	$C_{10}H_{19}NO_4$ (217.3)	0.9 (t, 3H, J = 6.5); 1.1–1.5 (m, 9H); 2.4–2.7 (m, 3H); 4.15 (q, 2H, J = 7); 4.50 (m, 2H)
2f	74	119–120/ 1.25	$C_{10}H_{19}NO_4$ (217.3)	0.9 (m, 6H); 1.22 (t, 3H, J = 7); 1.3–1.65 (m, 3H); 2.3–2.5 (m, 2H); 2.5–2.9 (m, 1H); 4.12 (q, 2H, J = 7); 4.4–4.6 (m, 2H)
2g	66	103–104/ 0.75	$C_{10}H_{19}NO_4$ (217.3)	0.95 (m, 6H); 1.28 (t, 3H, J = 7); 1.45–1.80 (m, 1H); 2.40 (d, 2H, J = 6.5); 4.15 (q, 2H, J = 7); 4.50 (d, 2H, J = 6.5)
2h	40	115–119/ 1	$C_{10}H_{19}NO_4$ (217.3)	0.95 (s, 9H); 1.25 (t, 3H, J = 7); 2.4–2.8 (m, 3H); 4.15 (q, 2H, J = 7); 4.4–4.7 (m, 2H)

[a] Yields of isolated pure products; not optimized and based on a single experiment.

[b] Satisfactory microanalyses obtained: C ±0.39, H ±0.23, N ±0.29.

Although the aliphatic nitro compounds are usually reduced either by high-pressure catalaytic hydrogenation,[10] by metal-catalyzed transfer hydrogenation,[11] or by newly-introduced hydrogenolysis methods with ammonium formate[12] or sodium borohydride[13] and palladium as catalyst, we have found that 4-nitrocarboxylic esters can be reduced almost quantitatively to the corresponding 4-aminocarboxylic esters by hydrogenation using 10% palladium on carbon as catalyst in acetic acid at room temperature and atmospheric pressure. The amino esters produced were subjected to acid hydrolysis to afford the title compounds **3a–h** in good yields (Table 2). This procedure provides access to a variety of 3-alkyl-4-aminobutanoic acids **3**, and thus is advantageous in comparison to methods previously used. Preliminary results indicate that compounds **3** are alternate substrates for the enzyme γ-aminobutyric acid aminotransferase.

All reagents were purchased from Aldrich Chemical Co. and were used without further purification. All solvents were dried under standard conditions if necessary. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Microanalyses were performed by Galbraith Laboratories, Knoxville, TN. ^{1}H-NMR spectra were recorded at 90 MHz on a Varian EM-390 spectrometer.

Ethyl 4,4-Dimethyl-2-pentenoate (1h):

Lithium bis(trimethylsilylamide) (50 mL of a 1 M solution in THF, 50 mmol) is placed in a dried, argon-filled round-bottomed flask equipped with magnetic stirrer and cooled to −78 °C, then EtOAc (4.92 mL, 50 mmol) is syringed in, and the mixture is stirred for 20 min. 2,2-Dimethylpropanal (5.5 mL, 50 mmol) is syringed into the solution. After 20 min, the reaction is quenched with 20% aq. HCl (10 mL), allowed to reach r.t., and EtOAc (50 mL) is added. The organic phase is washed with H_2O, dried ($MgSO_4$), and evaporated to give crude ethyl

Table 2. Amino Acids **3a–h** Prepared

Compound	Yield[a] (%)	mp (°C) (H_2O/ EtOH)	Molecular Formula[b] or Lit. mp (°C)	^{1}H-NMR (D_2O/DSS)[c] δ, J(Hz)
3a	83	204	174[2], 199[3]	1.05 (d, 3H, J = 7); 2.1–2.4 (m, 3H); 2.9–3.1 (m, 2H)
3b	84	203	178–180[4]	0.95 (t, 3H, J = 7); 1.3–1.65 (m, 2H); 1.9–2.3 (m, 1H); 2.35 (d, 2H, J = 6.5); 3.05 (d, 2H, J = 6)
3c	80	195–197	195[4]	0.95 (t, 3H, J = 6); 1.2–1.5 (m, 4H); 2.0–2.4 (m, 3H); 3.0 (d, 2H, J = 6.5)
3d	86	190–191	$C_7H_{15}NO_2$ (145.2)	0.95 (m, 6H); 1.5–2.1 (m, 2H); 2.25–2.50 (m, 2H); 2.9–3.1 (m, 2H)
3e	86	181–182	$C_8H_{17}NO_2$ (159.2)	0.9 (t, 3H, J = 7); 1.1–1.4 (m, 6H); 1.8–2.3 (m, 3H); 3.0 (d, 2H, J = 6)
3f	81	173–174	$C_8H_{17}NO_2$ (159.2)	0.9 (m, 6H); 1.1–1.35 (m, 3H); 2.0–2.4 (m, 3H); 2.9–3.1 (m, 2H)
3g	88	184–185	$C_8H_{17}NO_2$ (159.2)	0.95 (d, 6H, J = 6.5); 1.0–1.25 (m, 2H); 1.35–1.60 (m, 1H); 2.0–2.35 (m, 3H); 2.95 (d, 2H, J = 6)
3h	78	197–198	$C_8H_{17}NO_2$ (159.2)	0.95 (s, 9H); 1.75–2.10 (m, 1H); 2.3–2.6 (m, 2H); 3.2–3.4 (m, 2H)

[a] Yield of isolated pure product.

[b] Satisfactory microanalyses obtained: C ±0.27, H ±0.27, N ±0.18.

[c] DSS = 3-(trimethylsilyl)propanoic-2,2,3,3-d_4 acid, sodium salt.

3-hydroxy-4,4-dimethylbutanoate (yield: 7.7 g, 88%) [^{1}H-NMR ($CDCl_3$/TMS) $\delta = 0.95$ (s, 9H); 1.30 (t, 3H, $J = 7$ Hz); 2.5 (m, 2H); 3.45 (s, 1H); 3.75 (m, 2H); 4.25 (q, 2H, $J = 7$ Hz)]. The hydroxy ester is dissolved in pyridine (35 mL), this solution is cooled to 5 °C and $POCl_3$ (4.8 mL, 50 mmol) is added dropwise, with stirring. The mixture is kept for 3 h at room temperature, for 1 h at 100 °C, then poured onto crushed ice (100 g). The product is extracted with Et_2O (3 x 50 mL), the extract is washed with 2N aq. HCl (50 mL) and H_2O (50 mL), dried ($MgSO_4$), and distilled under reduced pressure: yield: 5.1 g (74%); bp 62 °C/9 Torr.

$C_9H_{16}O_2$	calc.	C 61.19	H 10.32
(156.2)	found	61.02	10.22

^{1}H-NMR ($CDCl_3$/TMS): $\delta = 1.1$ (s, 9H); 1.25 (t, 3H, $J = 7$ Hz); 4.20 (q, 2H, $J = 7$ Hz); 5.75 (d, 1H, $J = 16.5$ Hz); 7.0 (d, 1H, $J = 16.5$ Hz).

Ethyl 3-Alkyl-4-nitrobutanoates (Ethyl 3-Nitromethylalkanoates) 2a–h; General Procedure:

In a dry, argon-filled round-bottomed flask, fitted with magnetic stirrer, the appropriate ethyl 2-alkenoate **1a–h** (25 mmol) is dissolved in nitromethane (6.7 mL, 125 mmol) and 1,1,3,3-tetramethylguanidine (0.62 mL, 5 mmol) is added. In the case of **1h**, DBU (3.8 g, 25 mmol) is added instead of the guanidine derivative. The solution is stirred at r.t. for 48 h. Then, Et_2O (50 mL) is added, and the organic phase is washed with 1N aq. HCl (25 mL) and H_2O (25 mL), and dried ($MgSO_4$). The solvent is evaporated and the residue is distilled under reduced pressure (Table 1).

3-Alkyl-4-aminobutanoic Acids (3-Aminomethylalkanoic Acids) 3a–h; General Procedure:

A solution of the appropriate ethyl 3-alkyl-4-nitrobutanoate **2a–h** (5 mmol) in AcOH (15 mL) is hydrogenated over 10% Pd–C (100 mg) for 2–4 h at ambient temperature and pressure. The catalyst is then filtered off, and the filtrate is evaporated under reduced pressure. The residue is dissolved in 6N aq. HCl (20 mL) and refluxed for 3 h. Evaporation to dryness under reduced pressure yields a material which is purified by ion-exchange chromatography on Dowex 50W×8 (H^+ form) (eluting sequentially with H_2O till pH 7, then with 0.5N aq. NH_3). Fractions containing the amino acid **3** are collected, evaporated, and crystallized by dissolving the residue in a minimum amount of hot H_2O to which sufficient hot EtOH is added until just before crystallization begins (Table 2).

We gratefully acknowledge the National Institutes of Health (NS 15703) for financial support of this work.

Received: 23 January 1989; revised: 10 July 1989

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